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THE INFLUENCE OF QUININ AND UREA HYDROCHLORID, ETHYLHYDROCUPREIN, AND OTHER CINCHONA DERIVATIVES ON LEUKOCYTOSIS AND ON PHAGOCYTOSIS OF PNEUMOCOCCI IN VITRO *

STUDIES IN PNEUMONIA, IV.

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In the research concerning the action of cinchona derivatives in pneumonias, of which an additional phase is reported in the present paper, the question of the effect of these drugs on leukocytic, and especially on phagocytic action, was one of the problems early formulated. The clinician (S. S. C.) had long ago observed and recorded the fact that contrary to the general impression — and indeed to his own expectation — the administration of quinin, in any form and by any method, to a patient in the early stages of a lobar or lobular pneumonia, not only did not reduce the numbers or the apparent activity of the leukocytes, but — so far as one might judge in an infection normally accompanied with a progressive increase in the white-cell count — actually seemed to increase them. This apparent increase in leukocytosis was especially marked in cases treated by intramuscular injections of quinin and urea hydrochlorid, and several case reports illustrative of this fact have been published in the various clinical papers of the observer named.[1] The clinical observations on the differential count of leukocytes did not, however, show much change; or, at least, the changes were not sufficiently regular in the limited number of observations made, and under the great variety of clinical conditions, to warrant definite statement. On the whole, the increase seemed to affect chiefly the polymorphic and, to a less degree, the large mononuclear cells; but no stress could be, or had been, laid on this particular phase of the result.

In the later stages of lobar and lobular pneumonia, while there has

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[1] Jour. Infect. Dis., 1917, 20, p. 40. Am. Jour. Med. Sc., 1912, 143, pp. 42, 43. Jour. Am. Med. Assn., 1913, 61, p. 107 (Charts I and II). Internat. Clin., Series 22, 3, p. 62 (Chart II).

been no diminution of leukocytes that could be observed clinically, at least none that could be conclusively demonstrated, neither has there been any positively marked increase. Further studies will be directed toward these points, especially with regard to serologic types of microorganisms and in the light of the experimental facts reported in this paper.

The clinical observations referred to have, however, offered a sufficiently promising basis to warrant experimental study, especially when taken in connection with the general importance of phagocytosis in immunity in acute infections, particularly in those dependent on the pneumococcus. Other observers have preceded us in some portions of this field.

Tschistovitsch,[2] in 1904, found that in experimental pneumonia of the dog and in human pneumonia, phagocytosis was marked and he ascribed the crisis to this process. Kruse and Pansini[3] likewise described the phagocytosis of pneumococci in vivo; Lamar and Meltzer[4] found active phagocytosis of virulent pneumococci in the pulmonary exudates of experimentally produced pneumonias in dogs on the 2nd day following intrabronchial insufflation. On the 4th day practically all the cocci were found within cells. Similar results were reported by Winternitz and Hirschfelder[5] in the experimentally produced pneumonias of rabbits; these investigators also showed that depression of the leukocytic mechanism by injections of benzol greatly increased the mortality,[5] while injection of toluol, which tends to increase the number of leukocytes and cause hyperplastic changes in the bone marrow, was shown by Kline and Winternitz[6] to increase resistance in experimentally produced pneumococcus pneumonia. Winternitz and Kline[7] also demonstrated by further experiments, the rôle of the leukocyte in the immunity reaction in pneumonia, and by intravitam staining methods with trypan blue showed that up to the 7th day the majority of leukocytes in experimental lesions produced by virulent pneumococci were in a living state. Bull[8] also described the phagocytosis of virulent pneumococci in experimental pneumonia following their previous agglutination, and regards agglutination and subsequent phagocytosis as important factors in immunity in pneumococcus infections.

On the other hand, opsonic studies in vitro by Rosenow,[9] Tschistovitsch and Yurevitsch,[10] and Wadsworth[11] tended to show that virulent pneumococci are insusceptible to phagocytosis. Wadsworth[11] in a study of 25 pneumonic lungs found very few bacteria in the exudate and very little evidence of phagocytosis.

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[2] An. de l'Inst. Pasteur, 1890, 4, p. 285; 1904, 18, p. 304.
[3] Ztschr. f. Hyg. u. Infektionskr., 1891-1892, 11, p. 279.
[4] Jour. Exper. Med., 1912, 15, p. 133.
[5] Ibid., 1913, 17, p. 657.
[6] Ibid., 18, p. 50.
[7] Ibid., 1915, 21, pp. 311, 320.
[8] Ibid., 1915, 22, p. 457; 1916, 24, p. 7.
[9] Jour. Infect. Dis., 1907, 4, p. 285.
[10] Ann. de l'Inst. Pasteur, 1908, 22, p. 611.
[11] Jour. Exper. Med., 1912, 16, p. 54.

Newfeld and Haendel,[12] Rosenow,[13] Potter and Krumweide,[14] and Hektoen,[15] and others found that the opsonic activity of the serum and the phagocytic activity of the leukocytes were increased in pneumonia and other infectious diseases, but Seligmann and Klopstock,[16] Boettcher,[17] and Strouse[18] were unable to substantiate the claim that this change in the leukocytes themselves is an important factor. Strouse[19] through animal experiments concluded that altho opsonic immunity is produced in pneumonia, it is not the only means of defense possessed by the body, and by itself cannot explain the crisis.

The object of the present investigation was to determine the possible influence of quinin and urea hydrochlorid, ethylhydrocuprein, and other cinchona derivatives on leukocytosis and on phagocytosis of virulent pneumococci in vitro, as possibly shedding additional light on the action of these compounds in the treatment of the acute pneumonias. A report of further studies bearing on the influence of these derivatives on the phagocytosis of pneumococci in vivo will be given later. Manwaring,[20] Wilson,[21] and Grünspan[22] showed that strong dilutions of the quinin salts tend to inhibit phagocytosis of microorganisms in general, while weaker solutions act as stimulants. Wright[23] reported that ethylhydrocuprein administered to man does not increase the opsonic powers of the blood serum for pneumococci. Our experiments, on the other hand, show that weak dilutions of this derivative and other quinin compounds, materially facilitate the phagocytosis of virulent pneumococci.

METHOD OF STUDY

Washed rabbit leukocytes were used exclusively and all the work reported here was done with those obtained by intrapleural injection of sterile aleuronat. Leukocytes obtained in this manner proved more actively phagocytic than those in the peripheral blood, as pointed out by Tunnicliff some years ago.[24] After one washing with warm sterile salt solution the cells were resuspended in warm salt solution with an attempt to make the emulsions of successive experiments approximately equal in their content of polymorphonuclear neutrophiles.

Pure cultures of pneumococci belonging to Types I, II, and III were employed; most of the work was conducted with Type I.

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[12] Ztschr. f. Immunitätsf., 1909, 3, p. 159.

[13] Jour. Infect. Dis., 1906, 3, p. 683.

[14] Ibid., 1907, 4, p. 601.

[15] Jour. Am. Med. Assn., 1911, 57, p. 1579.

[16] Ztschr. f. Immunitätsf., 1909, 4, p. 103.

[17] Deutsch. Arch. f. klin. Med., 1909, 98, p. 93.

[18] Jour. Exper. Med., 1909, 11, p. 743.

[19] Ibid., 1911, 14, p. 109.

[20] Ibid., 1907, 9, p. 473.

[21] Am. Jour. Physiol., 1907, 19, p. 445.

[22] Centralbl. f. Bakteriol., I, O., 1908, 48, p. 444.

[23] On Pharmaco-therapy and Preventive Inoculation Applied to Pneumonia in the African Native, 1915, 16.

[24] Tr. Chicago Path. Soc., 1911, 8, p. 208.

The cocci were grown in blood dextrose broth for from 18 to 24 hours; carefully pipetted into centrifuge tubes; washed once with warm sterile salt solution and resuspended in salt solution until an emulsion was secured containing approximately a billion or more cocci to the cubic centimeter. As 24-hour cultures are always too sparse, this enriching by centrifugation was necessary.

The tests were conducted by mixing in small test tubes 0.1 c.c. of a dilution of quinin derivative or the serum of a rabbit after the administration of a compound, and 0.1 c.c. of the pneumococcus emulsion, and incubating the mixture at 37 C. for 1 hour. At the end of this time 0.1 c.c. of leukocytic emulsion was added to each tube, gently mixed, the whole reincubated for 1 hour, and then duplicate smears prepared and stained. During the second period of incubation the tubes were gently shaken several times to maintain a mixture of cells and cocci.

Two observers counted 100 cells on each slide, noting the percentage of phagocytes; no attempt was made to count the number of cocci within the cells. Numerous controls with cocci, salt solution, and leukocytes and with normal sera, cocci, and leukocytes, were included.

All dilutions were made with 0.85% sodium chlorid in distilled water.

SPONTANEOUS PHAGOCYTOSIS OF PNEUMOCOCCI

Under the conditions detailed, fairly well-marked spontaneous phagocytosis was noted with different cultures of various types of pneumococci, all of which possessed some virulence for mice and rabbits, as shown in Table 1.

All these cultures were considerably more virulent for white mice according to weight, by intraperitoneal injection.

TABLE 1

SPONTANEOUS PHAGOCYTOSIS OF TYPES OF PNEUMOCOCCI AND ITS RELATION TO VIRULENCE OF PNEUMOCOCCI FOR RABBITS (INTRAVENOUS INJECTION)

Types of Pneumococci	Virulence (72 hours) *	Phagocytic Indices
Type I (Culture A)	0.10 c.c.	3-5.5
Type I (Culture B)	0.02 c.c.	2-3.5
Type II (Culture A)	0.05 c.c.	2-4.0
Type II (Culture B)	0.02 c.c.	3-4.0
Type III (Culture A)	0.12 c.c.	3-5.5

* 24-hour dextrose-blood-broth cultures.

INFLUENCE OF CINCHONA DERIVATIVES ON PHAGOCYTOSIS OF PNEUMOCOCCI OF TYPES I, II, AND III

The results observed with 1:1000, 1:10,000, and 1:100,000 dilutions of quinin and urea hydrochlorid, ethylhydrocuprein hydrochlorid, and other cinchona derivatives, and virulent pneumococci belonging to the first three serologic types, are shown in Tables 2, 3, and 4.

Summary.—Allowance being made for spontaneous phagocytosis, our results indicate that cinchona derivatives facilitate the phagocytosis of pneumococci in vitro.

TABLE 2

BACTERIOTROPIC VALUE OF QUININ AND UREA HYDROCHLORID, ETHYLHYDROCUPREIN, AND OTHER CINCHONA DERIVATIVES FOR PNEUMOCOCCUS TYPE I *

Quinin Derivatives	Phagocytic Indices †		
	1:1000	1:10,000	1:100,000
Ethylhydrocuprein hydrochlorid	7.5	8.5	9.0
Quinin and urea hydrochlorid	7.0	9.0	9.0
Hydroquinin hydrochlorid	3.5	8.0	7.0
Quinin bisulfate	2.0	5.0	8.0
Quinin hydrochlorid	3.0	4.0	10.0
Quinin salicylate	3.0	5.5	8.0
Quinin (alkaloid)	2.0	3.0	6.0

* Virulence for rabbits in 72 hours by intravenous injection, about 0.1 c.c.
† Controls showed a spontaneous phagocytosis of 3-5.5%.

TABLE 3

BACTERIOTROPIC VALUE OF QUININ AND UREA HYDROCHLORID, ETHYLHYDROCUPREIN, AND OTHER CINCHONA DERIVATIVES FOR PNEUMOCOCCUS TYPE II *

Quinin Derivatives	Phagocytic Indices †		
	1:1000	1:10,000	1:100,000
Ethylhydrocuprein hydrochlorid	6.5	8.0	10.5
Quinin and urea hydrochlorid	8.0	9.5	11.0
Hydroquinin hydrochlorid	7.0	9.0	11.5
Quinin bisulfate	3.5	6.0	9.0
Quinin hydrochlorid	5.0	5.0	8.5
Quinin salicylate	6.0	7.0	9.5
Quinin (alkaloid)	3.0	3.5	4.5

* Virulence for rabbits in 72 hours by intravenous injection, about 0.03 c.c.
† Controls showed a spontaneous phagocytosis of about 3%.

Ethylhydrocuprein hydrochlorid facilitated the phagocytosis of all three types of pneumococci, especially Type III, but with Types I and II it was excelled by quinin and urea hydrochlorid.

Hydroquinin hydrochlorid and several quinin salts also facilitated

TABLE 4

BACTERIOTROPIC VALUE OF QUININ AND UREA HYDROCHLORID, ETHYLHYDROCUPREIN, AND OTHER CINCHONA DERIVATIVES FOR PNEUMOCOCCUS TYPE III *

Quinin Derivatives	Phagocytic Indices †		
	1:1000	1:10,000	1:100,000
Ethylhydrocuprein hydrochlorid	7.0	10.0	12.5
Quinin and urea hydrochlorid	6.5	8.0	9.5
Hydroquinin hydrochlorid	5.0	5.0	6.5
Quinin bisulfate	4.5	6.0	7.5
Quinin hydrochlorid	7.0	9.0	11.5
Quinin salicylate	5.0	7.5	9.5
Quinin (alkaloid)	4.0	4.5	5.5

* Virulence for rabbits in 72 hours by intravenous injection, about 0.12 c.c.
† Controls showed a spontaneous phagocytosis of about 4.5%.

phagocytosis to a greater or less degree. The degree of phagocytosis observed with the alkaloid alone was scarcely greater than the degree of spontaneous phagocytosis.

In all instances the highest dilution (1: 100,000) gave the best results. A dilution of 1: 100, particularly of the alkaloid quinin, produced marked degenerative changes in the leukocytes with practically no phagocytosis.

BACTERIOTROPIC ACTION OF THE SERA OF RABBITS RECEIVING INTRAMUSCULAR INJECTIONS OF QUININ COMPOUNDS AND OTHER CINCHONA DERIVATIVES

The bacteriotropic value of the sera of a number of normal rabbits was tested; then small doses of quinin and urea hydrochlorid, ethylhydrocuprein hydrochlorid and other cinchona derivatives were intramuscularly injected and similar tests of the sera made 2, 4, and 24 hours later.

The majority of these tests were conducted with a culture of pneumococcus belonging to Type I, a few experiments having shown that with Types II and III similar results were to be observed.

The results of a number of experiments are shown in Tables 5 and 6. The quantities of the various cinchona derivatives injected are shown in the tables; also the degree of phagocytosis found with the normal sera before the injections had been made and at intervals of 2, 4, and 24 hours later. All of these sera were placed in a refrigerator over night and used the following day without inactivation by heat.

TABLE 5

BACTERIOTROPIC VALUE OF RABBIT SERA FOR PNEUMOCOCCUS TYPE I AFTER ADMINISTRATION OF VARIOUS CINCHONA DERIVATIVES

Test	Weight (gm.)	Amount per Kilo (gm.)	Before Injection		2 hr. After Injection		4 hr. After Injection		24 hr. After Injection	
			1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100
After Administration of Ethylhydrocuprein Hydrochlorid										
1	1355	.002	2.3	11.0	6.0	40.0	8.0	17.0	8.5	30.0
2	1700	.001	2.2	8.2	6.0	11.0	3.5	14.5	5.5	20.0
After Administration of Quinin and Urea Hydrochlorid										
1	1255	.002	3.2	5.0	17.5	23.5	10.5	11.5	8.0	14.0
2	1200	.001	2.1	6.2	14.0	17.0	14.0	16.0	10.0	9.0
After Administration of Hydroquinin Hydrochlorid										
1	1420	.002	4.0	6.1	4.0	10.0	11.0	13.0	9.0	14.0
2	1350	.001	4.0	9.0	5.0	8.0	4.0	6.0	3.0	3.5
After Administration of Quinin Hydrochlorid										
1	1400	.002	2.0	8.0	4.0	10.0	8.0	13.0	7.0	11.0
2	1560	.001	2.5	6.5	4.5	11.5	12.0	15.0	9.5	12.0

TABLE 6

BACTERIOTROPIC VALUE OF RABBIT SERA FOR PNEUMOCOCCI AFTER ADMINISTRATION OF ETHYLHYDROCUPREIN HYDROCHLORID

Test	Weight (gm.)	Amount per Kilo (gm.)	Before Injection		2 hr. After Injection		4 hr. After Injection		24 hr. After Injection	
			1:10	1:100	1:10	1:100	1:10	1:100	1:10	1:100
For Type II										
1	1600	.002	2.0	6.0	8.0	15.0	9.0	12.0	7.0	13.5
2	1250	.001	2.0	8.0	6.5	12.0	7.5	11.5	6.5	12.0
For Type III										
1	1700	.002	1.5	4.0	4.5	10.5	5.0	12.0	6.0	11.5
2	1350	.001	2.0	4.5	5.0	11.0	4.5	10.5	4.0	10.0

The quantities of cinchona derivatives injected were relatively small and corresponded to doses of 0.12 and 0.06 gm., respectively, per 60 kilos (about 125 pounds) of body weight.

Summary.—As shown in the tables, normal rabbit serum appeared to facilitate in some instances the phagocytosis of pneumococci. A spontaneous phagocytosis ranging from 3 to 5.5% was expected with these cultures; the 1: 100 dilutions of sera almost invariably yielded higher percentages of phagocytosis than the 1: 10 dilutions. The sera of normal rabbits varied in pneumococcotropic value under identical experimental conditions as shown in the different tables.

Two hours after the intramuscular injection of quinin and urea hydrochlorid, ethylhydrocuprein hydrochlorid, and other cinchona derivatives, the bacteriotropic value of the sera for pneumococci was appreciably increased. At the end of 24 hours the values were still higher than before injection, but usually subsiding. In practically all instances the dilutions of serum of 1: 100 gave higher values than those of 1: 10.

Quinin and urea hydrochlorid and ethylhydrocuprein hydrochlorid yielded particularly definite results, each surpassing the other at certain points. The results with hydroquinin hydrochlorid were much less marked.

As a general rule, the sera of those rabbits receiving the larger of the two doses of each compound, yielded the higher bacteriotropic values.

MECHANISM OF THE ACTION OF CINCHONA DERIVATIVES

When large numbers of pneumococci were exposed to dilutions of ethylhydrocuprein hydrochlorid, quinin and urea hydrochlorid, and hydroquinin hydrochlorid of 1: 1000 for 1 hour at 37 C., then washed 3 times with warm normal salt solution by centrifugation, and exposed to the leukocytes for an hour at 37 C., higher phagocytic indices were found than when the cocci were mixed with leukocytes without previous exposure to solutions of the cinchonics. These results may be ascribed to a lowering of the resistance of the cocci by the drugs, which in the case of ethylhydrocuprein, may have amounted to an actual killing of large numbers, as shown in bactericidal tests by the centrifuge method.[26]

Experiments conducted in the routine manner, by exposure of the cocci to dilutions of the cinchonics of 1: 1000, 1: 10,000, and 1: 100,000

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[25] Cohen, Kolmer, and Heist, Jour. Infect. Dis., 1917, 20, p. 40.

followed by the addition of leukocytes may be contrasted with similar experiments in which the cocci had been washed with warm normal salt solution before mixture with the leukocytes. Higher phagocytic indices were shown in the former series of tests, which would seem to indicate that the high dilutions of the quinin compounds stimulated the leukocytes in their phagocytic activity.

As previously mentioned, low dilutions of these compounds acted in an opposite manner, retarding phagocytosis through degenerative changes induced in the leukocytes.

INFLUENCE OF QUININ AND UREA HYDROCHLORID, ETHYLHYDROCUPREIN HYDROCHLORID, AND OTHER CINCHONICS ON THE TOTAL LEUKOCYTES

Intramuscular injections of cinchona derivatives dissolved in normal salt solution increased the total number of leukocytes in the peripheral blood of white rats.

After preliminary leukocyte counts had been made on 2 successive days of several series of rats, a number of quinin compounds were administered intramuscularly and intravenously in dosage according to body weight. Subsequent counts were made 2, 4, 24, 48, 72, and 96 hours later.

In all instances the rats were kept at ordinary room temperature and counts made after a period of fasting, in order to reduce to a minimum the influence of other factors.

Doses ranging from 0.03 to 0.001 gm. per kilo. of body weight in 0.5 c.c. of normal salt solution were injected into the muscles of the thigh.

Several controls, consisting of the intramuscular injection of normal salt solution to determine the influence of trauma alone, were included.

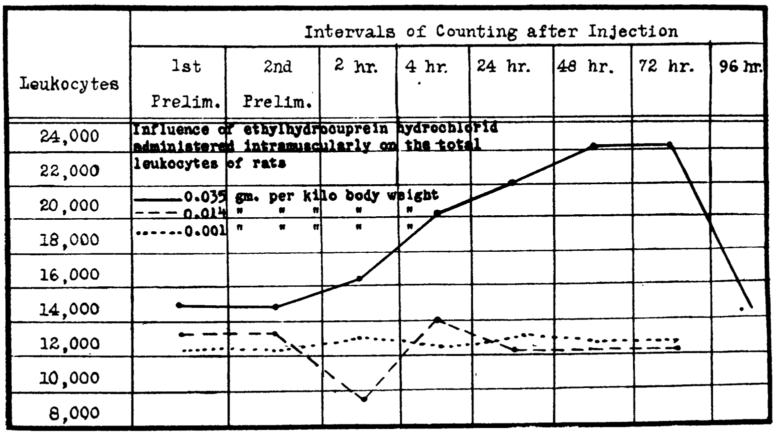
The influence of the following cinchonics was studied in this manner: ethylhydrocuprein hydrochlorid, and quinin and urea hydrochlorid, hydroquinin hydrochlorid, quinin hydrobromid, quinin lactate, quinin tannate, and quinin salicylate.

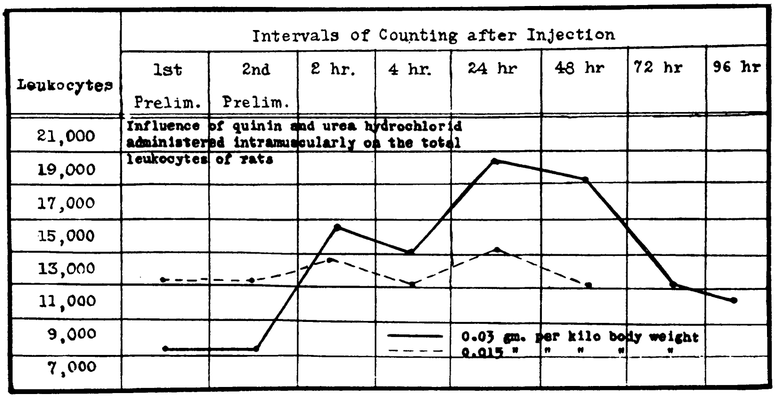
The results observed with the first three compounds are shown in the accompanying charts:

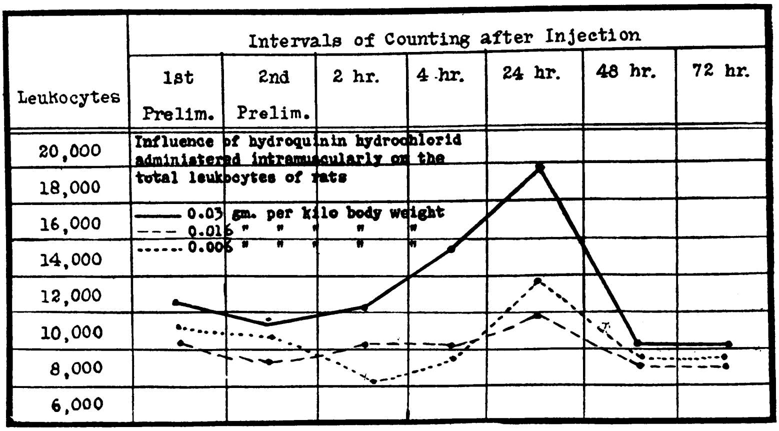
Summary.—As shown in the charts, the total leukocytes of normal rats varied from 8000 to 12,000 per cubic millimeter of blood, the number being usually nearer the latter figure. For this reason preliminary counts were necessary on each individual rat, and the effects were noted by comparing counts made after injection, with the preliminary counts.

The control rats generally showed a slight leukocytosis (increase of 1000 to 2000 cells), reaching the maximum at the end of 24 hours, followed by a rapid drop to normal.

As a general rule, the number of leukocytes was found to have


Leukocytes
Intervals of Counting after Injection
1st Prelim.
2nd Prelim.
2 hr.
4 hr.
24 hr.
48 hr.
72 hr.
96 hr.
24,000
22,000
20,000
18,000
16,000
14,000
12,000
10,000
8,000
Influence of ethylhydrocuprein hydrochlorid administered intramuscularly on the total leukocytes of rats
0.035 gm. per kilo body weight
0.014 " " " " "
0.001 " " " " "


Leukocytes
Intervals of Counting after Injection
1st Prelim.
2nd Prelim.
2 hr.
4 hr.
24 hr
48 hr
72 hr
96 hr
21,000
19,000
17,000
15,000
13,000
11,000
9,000
7,000
Influence of quinin and urea hydrochlorid administered intramuscularly on the total leukocytes of rats
0.03 gm. per kilo body weight
0.015 " " " " "


Leukocytes
Intervals of Counting after Injection
1st Prelim.
2nd Prelim.
2 hr.
4 hr.
24 hr.
48 hr.
72 hr.
20,000
18,000
16,000
14,000
12,000
10,000
8,000
6,000
Influence of hydroquinin hydrochlorid administered intramuscularly on the total leukocytes of rats
0.03 gm. per kilo body weight
0.016 " " " " "
0.008 " " " " "

increased 4 hours after injection with these compounds, with further increases up to 48 and 72 hours; after this time the number of leukocytes gradually dropped to normal.

The degree of leukocytosis generally bore a relation to the dose injected, the greatest rise in the number of leukocytes following the administration of the largest dose.

Ethylhydrocuprein hydrochlorid induced the highest degree of leukocytosis; but well-marked leukocytosis also followed the injection of quinin and urea hydrochlorid and hydroquinin hydrochlorid. Quinin lactate and quinin salicylate produced lesser degrees of leukocytosis.

The intravenous injection of these compounds produced lesser degrees of leukocytosis; local irritation due to the deposit of the compounds in the tissues was probably a cause for the higher leukocytosis noted with the intramuscular injections.

CONCLUSIONS

Pneumococci possessing some degree of virulence for rabbits and mice may undergo spontaneous phagocytosis by the exudative leukocytes of rabbits.

Ethylhydrocuprein hydrochlorid, quinin and urea hydrochlorid, and other compounds or derivatives of quinin in high dilutions, accelerate the phagocytosis of pneumococci by rabbit leukocytes.

Low dilutions of cinchona derivatives retard phagocytosis and induce degenerative changes in leukocytes.

The administration of ethylhydrocuprein hydrochlorid, quinin and urea hydrochlorid, and other quinin derivatives to rabbits by intramuscular injection increases the phagocytic powers of the sera for pneumococci.

It is probable that these quinin derivatives in high dilution accelerate phagocytosis by reducing the virulence and resistance of the pneumococci and also by stimulating the phagocytic activities of the leukocytes.

The intramuscular injection of ethylhydrocuprein hydrochlorid, quinin and urea hydrochlorid, and other cinchona derivatives in rats increases the total number of leukocytes in the peripheral blood. Lesser degrees of leukocytosis follow the intravenous injection of these compounds.

These experiments indicate that probably a part of the curative effect of quinin and urea hydrochlorid, ethylhydrocuprein, and other cinchonics in pneumococcus infections is to be ascribed to their influence on phagocytosis.